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Reconstruction Methods for Improved Detection of
Recurrent Prostate Cancer

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13. ABSTRACT (Maximum 200 Words) It is generally recognized that ¹¹¹ In capromab pendetide (PS) scans are technically challenging to perform and interpret, particularly with regard to pelvic SPECT studies used to detect possible disease in the prostate fossa and pelvic lymph node (LN). The hypothesis of this proposal is that the superior spatial resolution methods would substantially aid in the detection and diagnosis of prostate cancer. To test our hypothesis, we propose five specific aims: (1) to develop simulation tools and methods that allow efficient generation of accurate ¹¹¹ In PS projection data from the human pelvic area, (2) to study the effects of 3 D image degrading factors on ¹¹¹ In PS SPECT images, (3) to develop 3D corrective image reconstruction methods for ¹¹¹ In PS SPECT that provide much improved image quality and quantitative accuracy by incorporating models of the 3D image degrading factors, (4) to evaluate the 3D corrective image reconstruction methods for clinical ¹¹¹ In PS SPECT studies using simulated patient data, and Hotelling and human observer studies, and (5) to evaluate the clinical efficacy of the corrective image reconstruction methods as applied to ¹¹¹ In PS SPECT using patient data.				
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INTRODUCTION

Prostate carcinoma, a leading cause for male cancer deaths, was estimated to result in 180,400 new cases and 31,900 deaths in the year 2000¹. Earlier detection of prostate cancer has resulted from screening with serum prostate-specific antigen (PSA), with detection of disease when it is more localized². In order to treat prostate cancer appropriately, it is essential to have accurate staging data. Clinicians try to determine tumor size and location, degree of periprostatic extension and whether bone and/or lymph node (LN) metastases are present. Imaging techniques routinely used for this purpose include transrectal ultrasound, pelvic CT and MRI, and radionuclide bone scanning. Despite these efforts, initial evaluation of pre-surgical patients leads to understaging in as high as 40 to 71% of patients³. Detection of LN metastases has been difficult, since LN involvement in prostate cancer is often associated with normal sized nodes. Since detection of LN disease with pelvic CT and MRI depends upon LN enlargement, neither of these modalities has been very successful in detecting the spread of prostate cancer to nodes (MRI slightly better than CT). Pooled data from four MRI series demonstrate an overall sensitivity of 42% and specificity of 98%⁴.

Imaging with ¹¹¹In capromab pendetide (PS), a monoclonal antibody agent utilizing an indium-labeled antibody to prostate-specific membrane antigen (present in increased amounts in prostate cancer cells) has proven useful in detecting LN metastases. It is particularly useful in the detection of recurrent prostate carcinoma in patients who have had radical prostatectomy for their disease, but who have increasing PSA levels indicating the presence of an additional tumor. In a multi-institutional study, ¹¹¹In PS scanning localized disease in 108 of 181 patients (60%) with uptake in the prostatic fossa in 62 patients (34%), pelvic LN in 40 patients (22%) and abdominal LN in 42 patients (23%)⁵. Results were evaluated for the prostate fossa by ultrasound guided biopsy: 59 patients had positive biopsies for recurrent tumor, but only 29 of these had positive scans for a sensitivity of 49%⁶. The investigators felt that the false negative scans were likely to be due to small tumor volume. Results are more difficult to confirm for disease outside the prostatic fossa, since the LN metastases will usually be too small for detection by CT or MRI.

It is generally recognized that ¹¹¹In PS scans are technically challenging to perform and interpret⁵, particularly with regard to the pelvic SPECT study used to detect possible disease in the prostate fossa and pelvic LN. Certainly part of this challenge is the detection of increased uptake in relatively small tumors in the pelvis.

In our preliminary study, we have demonstrated that corrective image reconstruction techniques that accurately correct for attenuation, collimator-detector response and scatter can significantly improve the quality and quantitative accuracy of ¹¹¹In PS SPECT images. The hypothesis of this proposal is that the superior spatial resolution, high image contrast, and much reduced image artifacts that result from the corrective SPECT image reconstruction methods would substantially aid in the detection and diagnosis of prostate cancer.

To test our hypothesis, we propose five specific aims: (1) to develop simulation tools and methods that allow efficient generation of accurate ¹¹¹In PS projection data from the human pelvic area, (2) to study the effects of 3D image degrading factors on ¹¹¹In PS SPECT images, (3) to develop 3D corrective image reconstruction methods for ¹¹¹In PS SPECT that provide much improved image quality and quantitative accuracy by incorporating models of the 3D image degrading factors, (4) to evaluate the 3D corrective image reconstruction methods for clinical ¹¹¹In PS SPECT studies using simulated populations of patient data, and Hotelling and human observer studies, and (5) to evaluate the clinical efficacy of the corrective image reconstruction methods as applied to ¹¹¹In PS SPECT using patient data.

BODY

As we discussed in our first year report, our entire laboratory relocated from the University of North Carolina at Chapel Hill (UNC-CH) to Johns Hopkins University (JHU) in July 1, 2002. We had an

extremely smooth transition and were able to continue the research project with minimal interruption. In the following, we describe the progress we have made during Year 1 of the project. The report addresses the specific tasks for Year 1 listed in the original proposal.

Task 1. To develop simulation tools and methods for ^{111}In prostate SPECT (Months 1-18):

- a. Extend the realistic NCAT phantom to include the pelvic region of the body (Months 1-12)
- b. Continue the development of a Monte Carlo simulation method that generates realistic projection data from the NCAT phantom with accurate models of the multiple photon emissions from ^{111}In , their attenuation and scatter in the body, and the geometric, penetration and scatter response of the collimator (Months 4-18)

Accomplishments:

1. We have completed Task 1(a) in Year 1 as reported in the 1st year report.
2. As reported in the 1st year report, we have made significant progress of Task 1 (b) of the original proposal. We have extended the 3D NCAT (NRUB-based CArdiac Torso) phantom developed in our laboratory to include the pelvic region for this grant research. Also, we reported our initial work in the development of new techniques to speed up the Monte Carlo simulation methods.
3. In Year 2, we completed both parts (a) and (b) of Task 1. We determined the average uptakes of ^{111}In capromab pendetide (PS) in different organs based on the preliminary patient SPECT studies we acquired at UNC-CH before the present research grant started. The average uptakes in the different organs were used in the 3D NCAT phantom to develop an average ^{111}In PS radioactivity distribution phantom. A 3D attenuation distribution phantom was determined by assigning average attenuation coefficients for the ^{111}In photon energies to the bone structures and all tissues organs of the 3D NCAT phantom. Also, we identify the 26 possible sites of lymph nodes in the pelvic region. Figure 1 shows sample transaxial slices from the ^{111}In PS radioactivity distribution phantom with several of the lymph node sites. Figure 2 shows the corresponding transaxial slices from the attenuation distribution phantom.

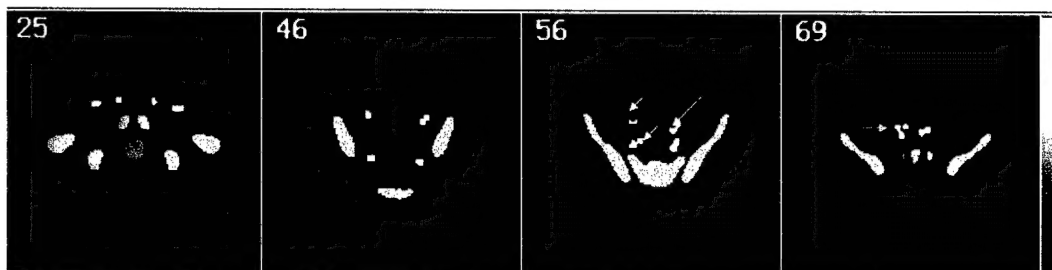


Figure 1. Sample transaxial slices of the ^{111}In PS radioactivity distribution phantom showing the prostate in the first slice, and with colored arrows pointing to several lymph nodes.

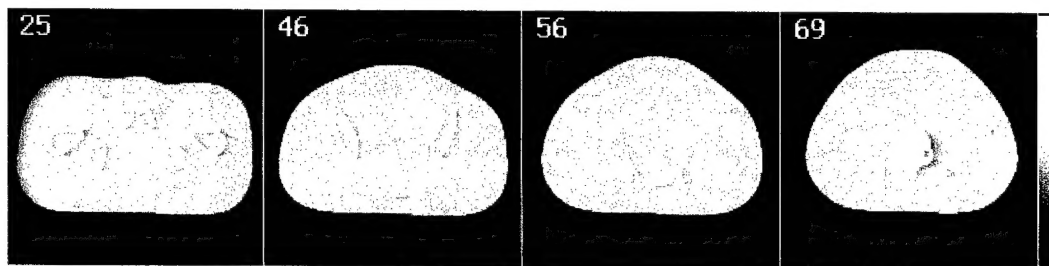


Figure 2. Sample transaxial slices from the attenuation distribution phantom.

4. Also in Year 2, we completed the development of a fast simulation method to generate projection data of the 3D ^{111}In PS phantom that accurately models the effects of photon attenuation and scatter within

the phantom and the full collimator-detector response characteristics that include geometric, penetration and scatter components. The fast simulation method consists of two steps. In the first step, the SimSET Monte Carlo code developed at the University of Washington was used to simulate photon transport within the 3D phantom based on the ^{111}In PS uptake and attenuation distributions. The histories of photons exiting the phantom were saved in a history file for later use. In the second step, we apply a predetermined angular response function (ARF) specific for the collimator-detector used in the data acquisition and the ^{111}In photon energies to each photon in the photon history file. The ARF is the point source response function of the collimator-detector at the ^{111}In photon energies in angular increment. It is generated from the MCNP Monte Carlo code and includes the geometric, penetration and scatter components of the collimator-detector response.

As shown in Figure 3, the predetermined ARF accurately models the collimator-detector response as compared to the results from Monte Carlo simulation using the MCNP code. Table 1 shows that the ARF method is 27 times faster than the MCNP Monte Carlo method in processing 1 billion photon histories from the history file to simulate the image of an In-111 point source using a GE medium energy (ME) collimator. Since the ARF method is less susceptible to noise fluctuations due to the limited number of photon histories, there is an additional saving in processing time with the ARF method if the same image quality is used in the comparison. In the later case, the total saving in processing time with the ARF methods is 410 times that of the MCNP method. This is a critical development to allow us to perform the full simulation with a reasonable amount of computational time.

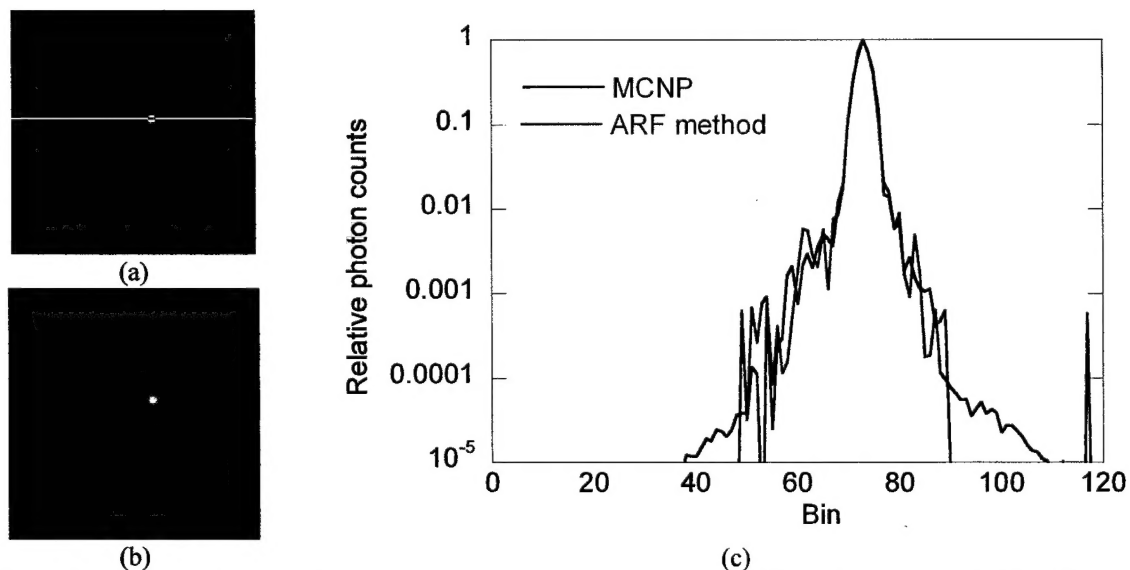


Figure 3. Projection images of an In-111 point source obtained using a GE medium energy (ME) collimator using (a) the MCNP Monte Carlo simulation code and (b) the fast ARF method. To obtain the same image quality, the number of the photons simulated using MCNP is 15 times that using the ARF. (c) Comparison of the horizontal profiles through the projection images.

Table 1. Comparison of the CPU times in simulating the collimator-detector response using the MCNP Monte Carlo code and the new ARF method

	Simulation Method	
	MCNP	ARF
Processing time to simulate 1 billion photon histories	2,873 sec	105 sec
Number of photon histories required to obtain the same image quality	15 billion	1 billion
Total CPU time	12 hours	105 sec

Figure 4 show sample projection images generated from the ^{111}In PS radioactivity and attenuation distributions generated from the 3D NCAT phantom using the fast simulation methods described above. They demonstrate the effectiveness of the simulation method to generate data that realistically mimic those acquired from an average patient.

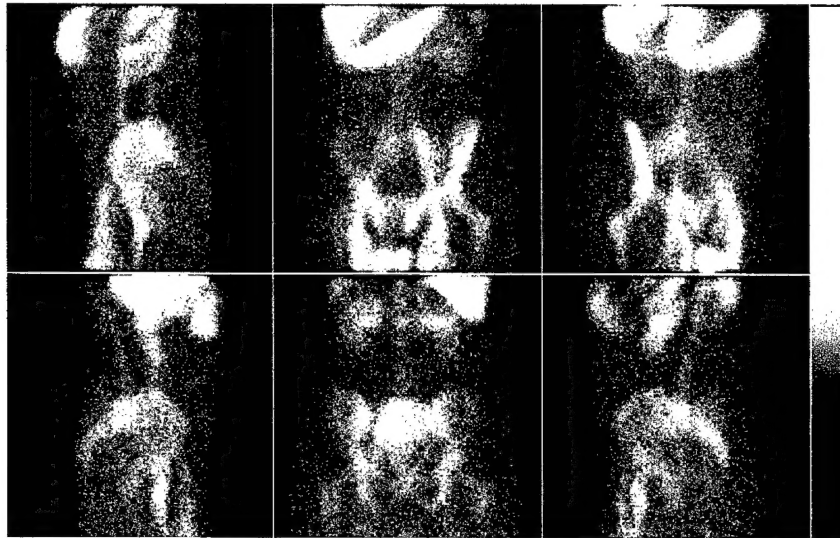


Figure 4. Simulated projection data of the ^{111}In PS radioactivity and attenuation distribution phantoms, showing 6 views over a 360° range. As described in the text, they were generated using the SimSET Monte Carlo code to simulate photon transport through the phantom and the Angular Response Function (ARF) to simulate the full collimator-detector response characteristics.

The data for each photopeak of ^{111}In were generated separately, and then summed.

- Task 2. To study the effects of 3D image degrading factors on ^{111}In prostate SPECT (Months 4-21):
- Study the effect of photon attenuation in the patient's body on ^{111}In SPECT images (Months 4-12)
 - Study the effects of photon scatter in patient's body on ^{111}In SPECT images (Months 7-15)
 - Study the effects of collimator-detector response on ^{111}In SPECT images (Months 10-18)

Accomplishments:

- As shown in Figure 3, in Year 2 we have developed a fast Monte Carlo method that allows us to generate projection data that accurately model the effects of photon attenuation and scatter within the phantom and the full characteristics of the collimator-detector used. This is a very complicated process. The successful implementation of this fast Monte Carlo simulation capability also allows us to generate projection datasets that selectively include the effects of photon attenuation and/or scatter and/or characteristics of the collimator-detector used in the data acquisition. These datasets can be generated with much faster speed than those that include all the physical instrumentation effects.
- The datasets that include the selected physical and instrumentation effects are reconstructed, organized and studied. The reconstructed images allow us to study the effects of photon attenuation and scatter in the patient's body and of the collimator-detector response characteristics on the ^{111}In SPECT images. Figure 5 shows an example of reconstructed images from the simulation study where the projection data were generated using the simulation method described above and include the effects of photon attenuation and scatter in the patient and the full imaging characteristics of the collimator-detector system. No compensation was used in the conventional filtered backprojection (FBP) reconstruction algorithm and the iterative OS-EM

algorithm. The reconstruction images demonstrate the effects of photon attenuation and scatter and the collimator-detector response. Also, they demonstrate the iterative OS-EM reconstruction algorithm without compensation give similar reconstructed image artifacts as the conventional FBP algorithm.

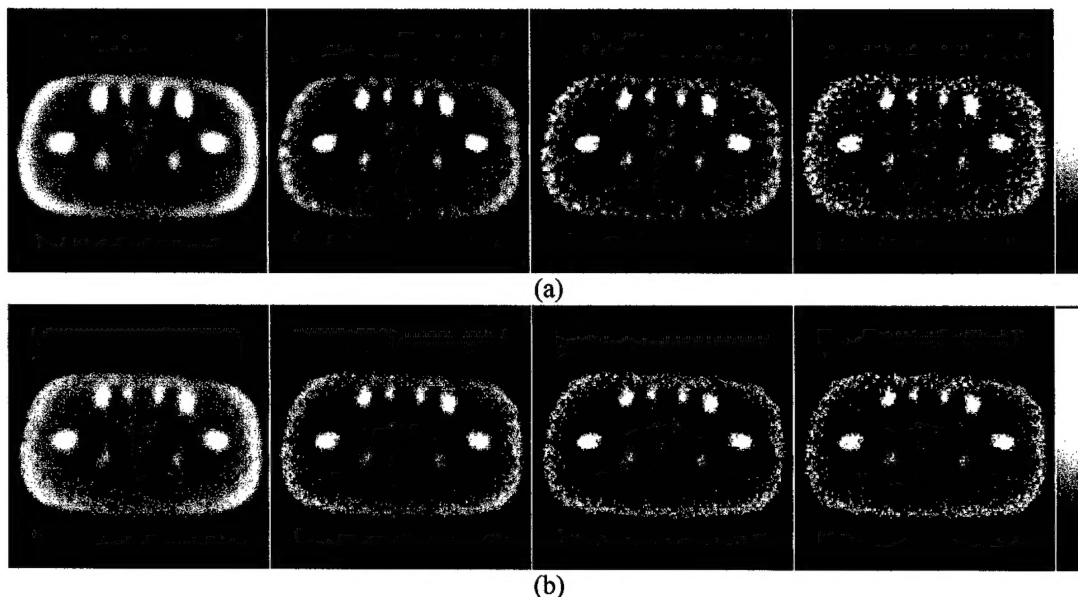


Figure 5. (a) Transaxial reconstructed images from a sample slice through the 3D NCAT phantom obtained using the filtered backprojection algorithm without any compensation. The images were post-filtered using a Butterworth filter with order 8 and, from left to right, filter cutoffs of 0.10, 0.20, 0.30 and 0.40 cycles/pixel, respectively. (b) Transaxial reconstructed images from the sample slice obtained using the iterative OS-EM algorithm without any compensation at, from left to right, the 1st, 2nd, 3rd and 4th iteration, respectively. Twelve subsets were used in the OS-EM algorithm.

Task 3. *To continue the development of 3D corrective image reconstruction methods for ^{111}In prostate SPECT that provide much improved image quality and quantitative accuracy by incorporating models of the 3D image degrading factors (Month 7-24):*

- a. *To use results from Task 2 to guide the development of methods to incorporate accurate models of image degrading factors in iterative and non-iterative 3D image reconstruction methods (Months 7-24)*

Accomplishments:

1. We have accomplished the development of 3D corrective image reconstruction methods for ^{111}In prostate SPECT that provide much improved image quality and quantitative accuracy by incorporating models of the 3D image degrading factors. The 3D corrective image reconstruction methods incorporate accurate compensation of photon attenuation and scatter in the patient and the full characteristics of the collimator-detector response in the iterative OS-EM algorithm. The compensation methods utilize the results from Task 2 to guide the development
2. In Figure 6, we show the improvements in reconstructed image quality as the image corrective image reconstruction method incorporates different individual and combination of image degrading effects including photon attenuation and scatter in the patient and the full image characteristics of the collimator-detector response. Here results from a sample slice through the 3D NCAT phantom and noise-free simulated projection data as described in Task 2 were used.

3. In Figure 7, results from simulated noisy projection data from four sample slices through the 3D NCAT phantom and at three noise levels were shown. They demonstrate the ability of the corrective image reconstruction methods in processing realistic data as compared with the conventional FBP image reconstruction method without any compensation.

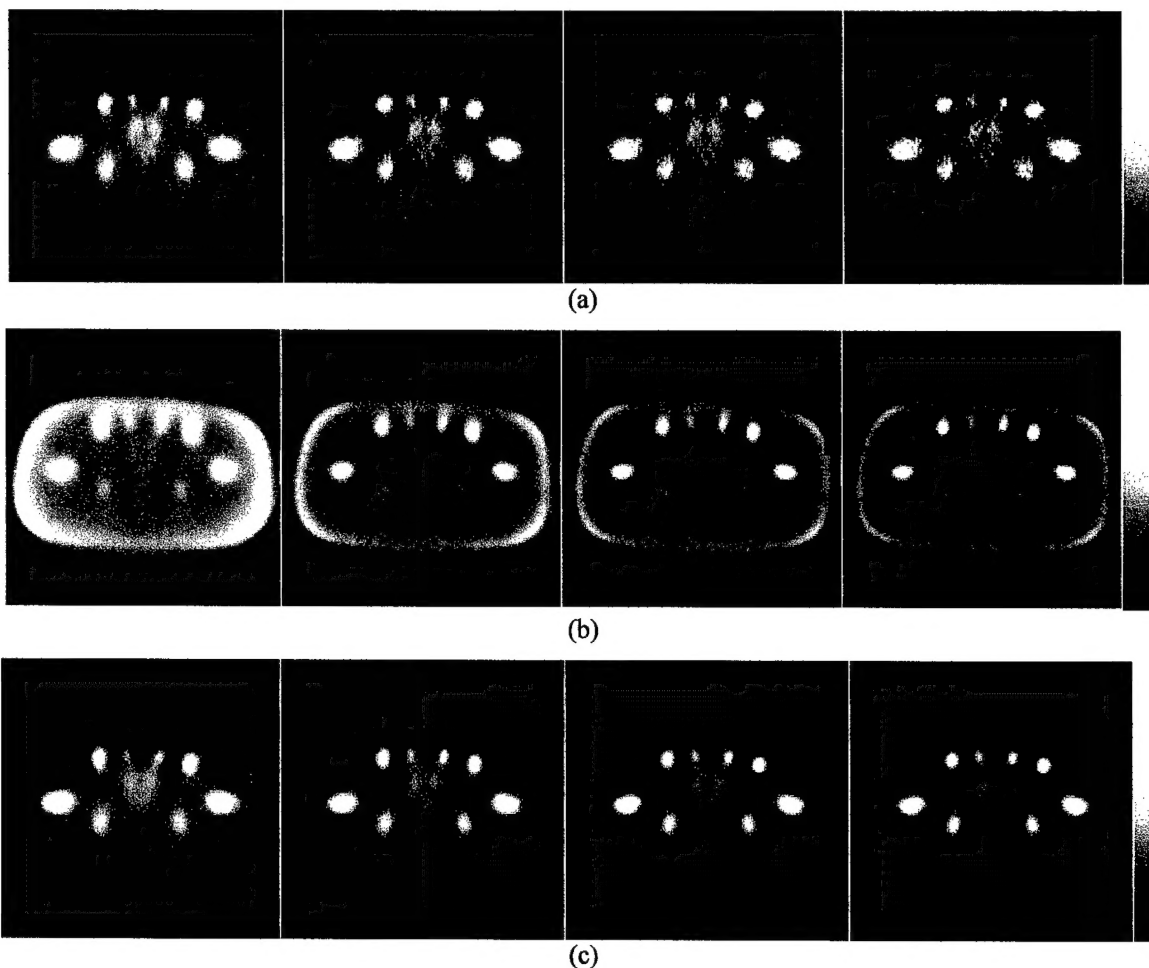


Figure 6. Transaxial reconstructed images of a sample slice through the 3D NCAT phantom using simulated noise-free projection data and corrective reconstruction method with compensation of individual and combination of image degrading effects. (a) Reconstructed images obtained using the iterative OS-EM algorithm with compensation of photon attenuation alone at, from left to right, 1st, 2nd, 3rd, and 4th iterations, respectively. (b) Reconstructed images obtained using the iterative OS-EM algorithm with compensation of the full collimator-detector response alone at, from left to right, 1st, 2nd, 3rd, and 4th iterations, respectively. (c) Reconstructed images obtained using the iterative OS-EM algorithm with compensation of both photon attenuation and full collimator-detector response at, from left to right, 1st, 2nd, 3rd, and 4th iterations, respectively. Twelve subsets were used in the OS-EM algorithm.

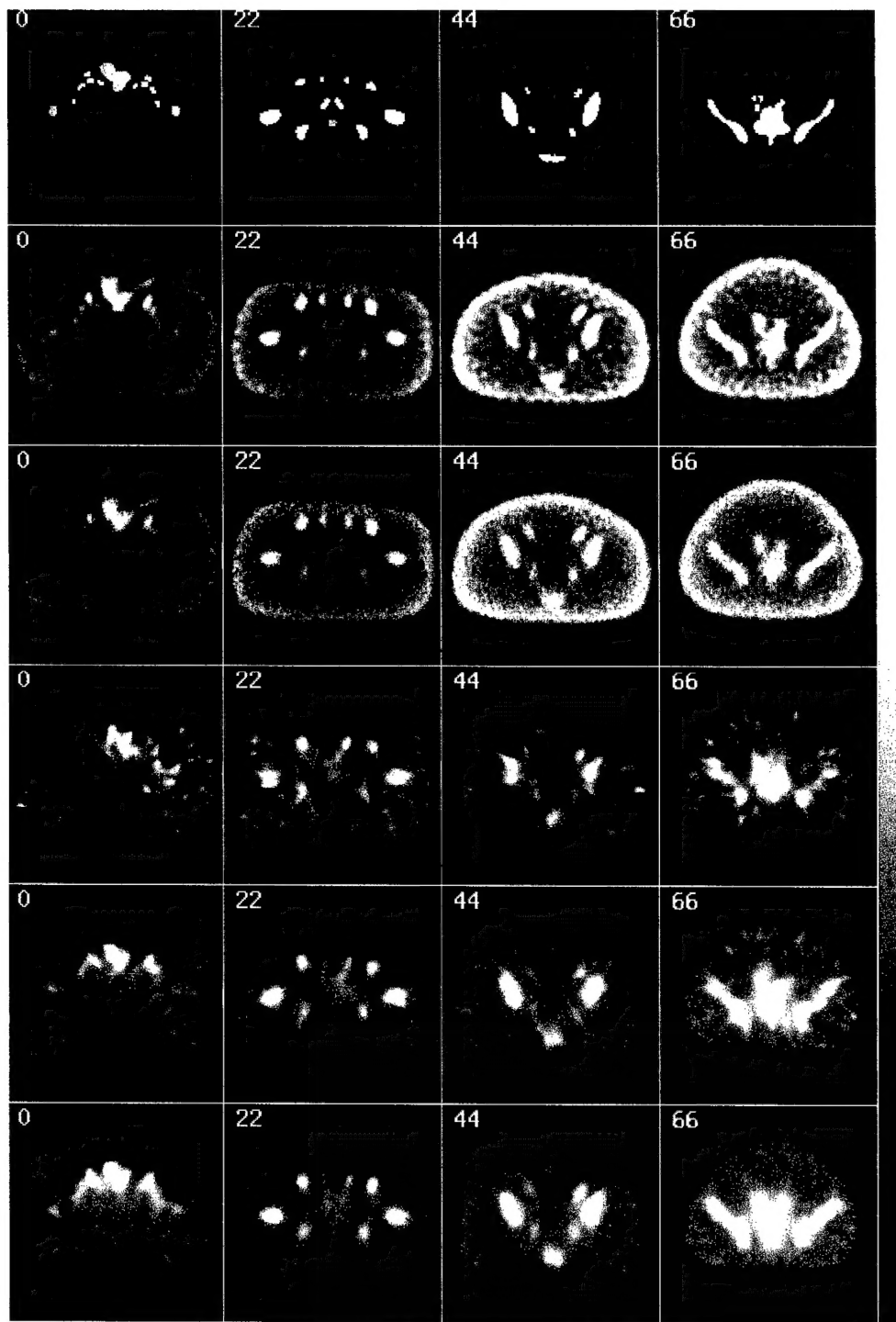


Figure 7. Results from simulation study to evaluate the effectiveness of the corrective image reconstruction method in improving the quality and quantitative accuracy of ^{111}In PS SPECT images. The four columns represent results from four different slices through the 3D NCAT phantom. *First Row*: The activity distribution of the image slices. *Second Row*: Transaxial reconstructed images obtained using the FBP algorithm and a Butterworth post-filter with order 8 and cut-off frequency at 0.2 cycles/pixel. *Third Row*: Transaxial reconstructed images obtained using the iterative OS-EM algorithm with no compensation. *Fourth Row*: Transaxial reconstructed images obtained using the iterative OS-EM with compensation for attenuation and the full CDR, applied to noisy projection data with 5,000 counts/slice. *Fifth Row*: Similar to the fourth row except with 20,000 counts/slice. *Sixth Row*: Similar to the fourth row except with 80,000 counts/slice. Six subsets were used in the OS-EM algorithm.

Task 4. *To evaluate the 3D corrective image reconstruction methods for ^{111}In prostate SPECT using simulated populations of patient data, and Hotelling and human observers (Month 13-36):*

- a. *Evaluate the 3D corrective imaging reconstruction methods as applied to ^{111}In prostate SPECT using Hotelling observers and ROC analysis methods (Months 13-36)*
- b. *Evaluate the 3D corrective imaging reconstruction methods as applied to ^{111}In prostate SPECT using human observers and ROC analysis methods (Month 19-36)*

Accomplishments:

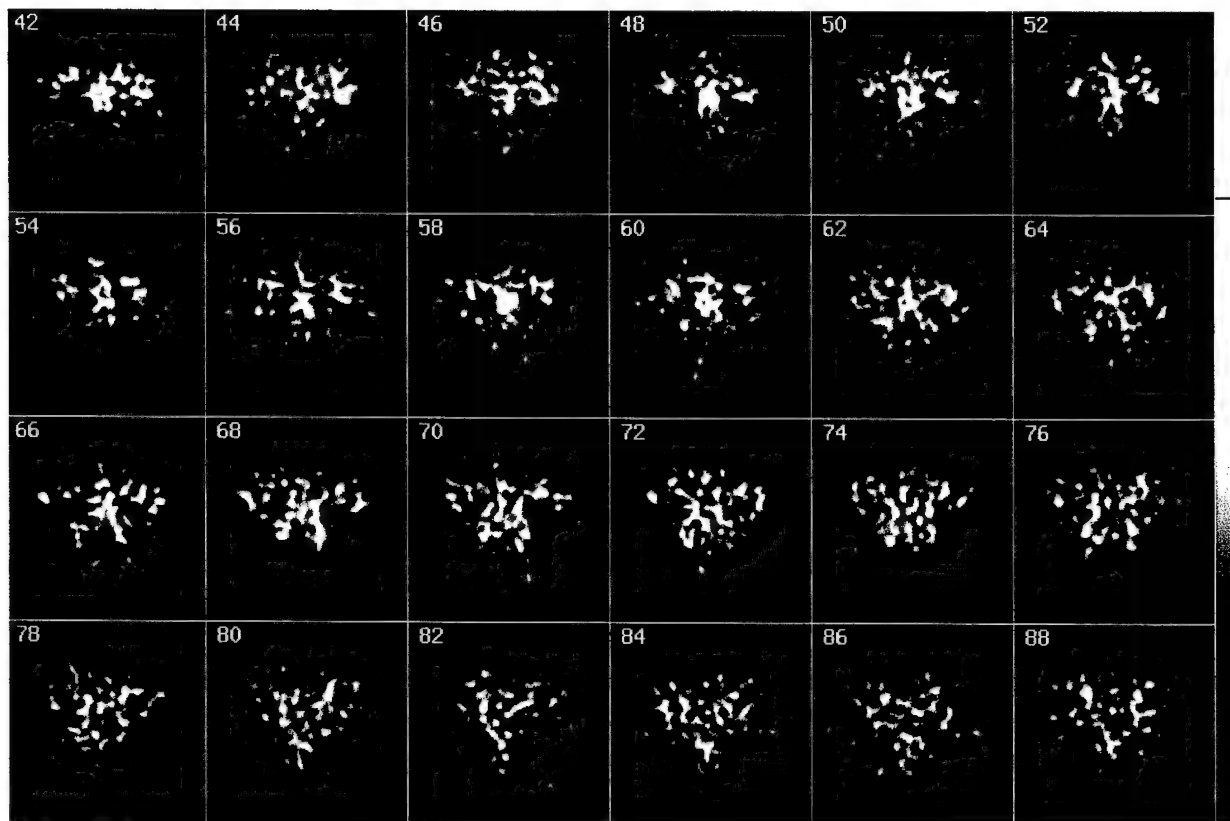
1. The results obtained in Task 3 are a crucial part in accomplishing Task 4. The capability of generating realistic projection data that mimic those obtained in the clinical settings assure the clinical applicability of our results. The development of the fast simulation methods allows us to accomplish the project within the grant funding period. We are in the process of designing the Hotelling and human observer experiments including the determination of the tasks of the observer study, the implementation of abnormal anatomy and abnormal ^{111}In PS uptakes in the 3D NCAT phantom, the development of experimental paradigm, and the determination of the number of datasets required in the observer study. We have begun simulating data required for the evaluation study and expect to have significant progress before the end of Year 2. In Year 3, we expect to perform full scale data simulation and to conduct the Hotelling and human observer studies.

Task 5. *To evaluate the clinical efficacy of the corrective image reconstruction methods using patient ^{111}In prostate SPECT data (Month 1-36):*

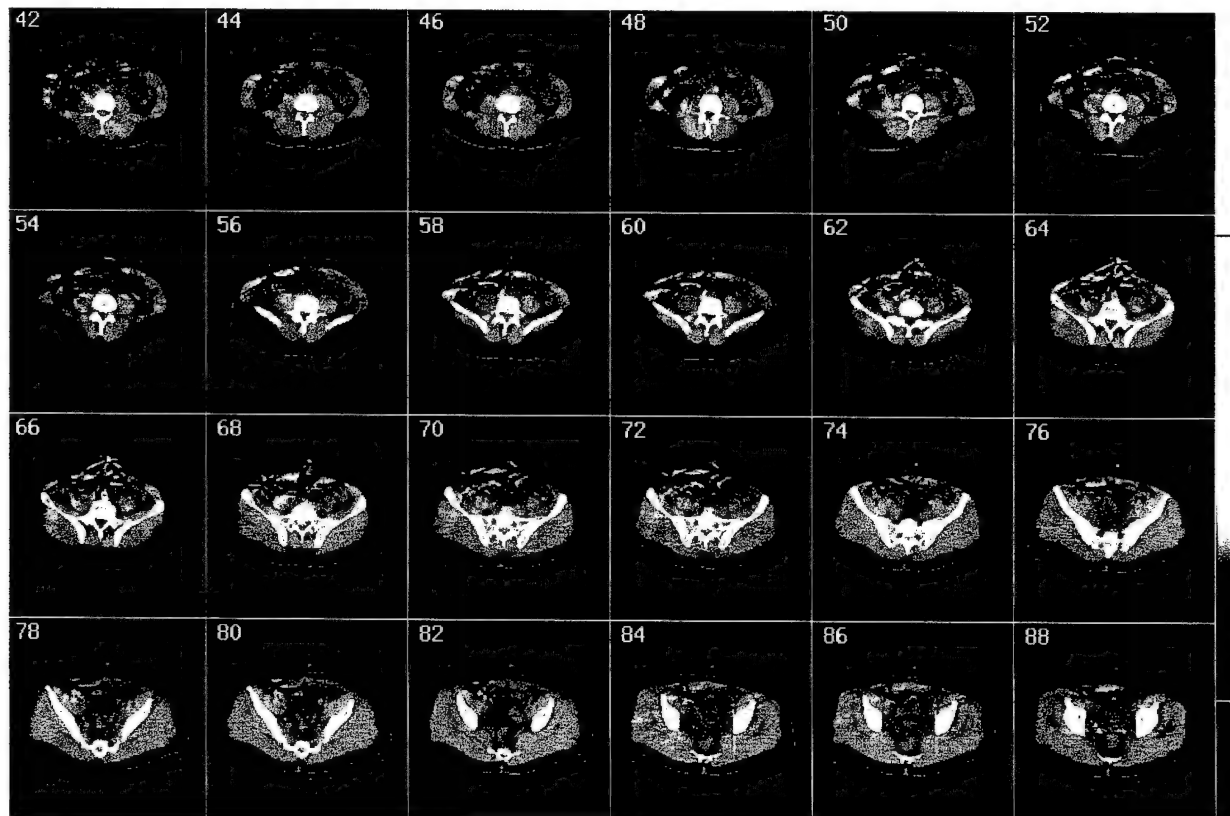
- a. *To set up the GE VG/Hawkeyes dual-head SPECT system for ^{111}In PS SPECT data acquisition from patients (Month 1-3)*
- b. *To acquire ^{111}In PS SPECT data acquisition from patients (Month 4-33)*
- c. *To process the patient ^{111}In PS SPECT data using the corrective image reconstruction methods developed in Task 3 (Month 4-33)*
- d. *To conduct clinical evaluation of the patient ^{111}In PS SPECT data (Month 13-33)*
- e. *Statistical analysis of evaluation data (Month 31-36)*

Accomplishments:

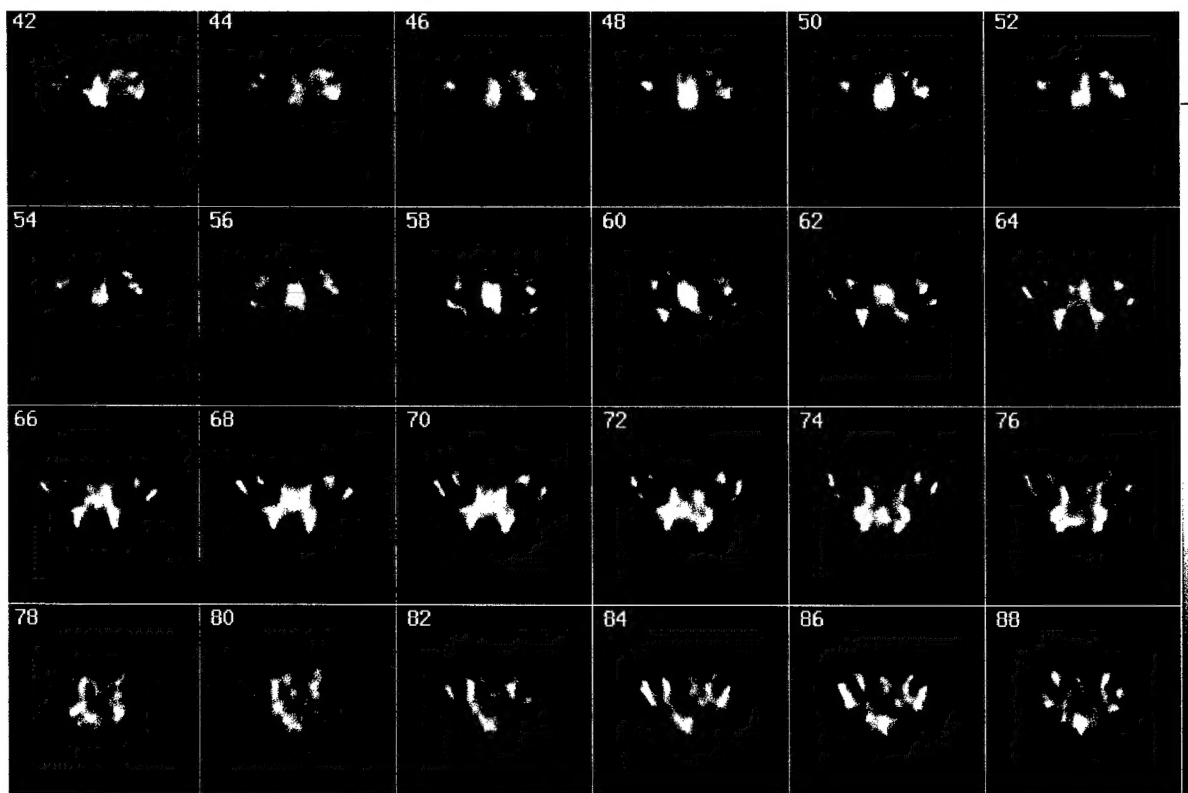
1. Task 5 (a) has been completed in Year 1.
2. We have obtained IRB approval since our laboratory relocated to Johns Hopkins University (JHU). During Year 2, we have worked with the nuclear medicine clinic at JHU to modify the ^{111}In PS SPECT data acquisition protocol to improve the quality of the acquired data. There is a slight delay in the clinical data acquisition due to the relocation and the application of the IRB. However, the official patient data acquisition and processing has begun. We have acquired data from 6 patient studies to-date. Figure 8 shows results from one of the patient datasets.



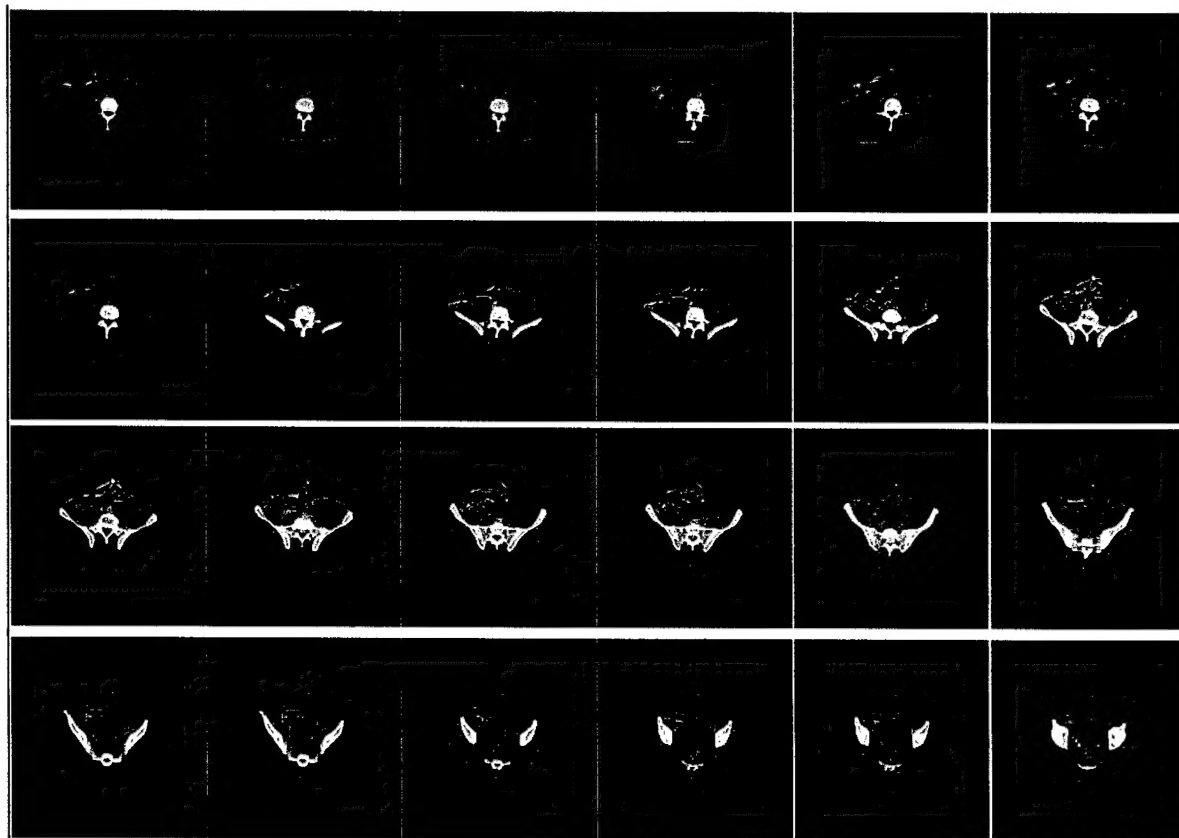
(a)



(b)



(c)



(d)

Figure 8. Results from one of the patient ^{111}In PS SPECT studies obtained using a GE VG dual-head SPECT system equipped with a Hawkeye x-ray CT unit. The patient was injected with 5 mCi of ^{111}In PS. The total data acquisition time was 35 minutes and a GE ME collimator was used. (a) Transaxial reconstructed images obtained using the conventional FBP reconstruction algorithm without any compensation. (b) Corresponding registered transmission CT images from the same patient. (c) Transaxial reconstructed images obtained using the iterative OS-EM algorithm with compensation of photon attenuation and scatter and the full collimator-detector response. Ten subsets and 5 iterations were used in the OS-EM reconstruction. Note the much improved image quality in terms of lower image noise and improved image resolution. (d) Fused SPECT/CT images.

KEY RESEARCH ACCOMPLISHMENTS

1. Completed extension of the realistic 3D NCAT phantom to include the pelvic region of the body. The extended phantom includes the prostate gland, bladder, key blood vessels and major lymph nodes in the pelvic region.
2. Completed the development of a fast simulation method of realistic ^{111}In PS projection data. The method is based on Monte Carlo simulation methods to simulation photon transport inside the phantom and the development of an angular response function (ARF) which accurately models the full imaging characteristics of the collimator-detector response function. The ARF is predetermined using Monte Carlo methods. The fast simulation method is 410 times faster than a straight Monte Carlo simulation method and provides the same accuracy and simulated image quality.
3. Completed the development of corrective image reconstruction methods that incorporate accurate compensation of photon attenuation and scatter in the patient and an accurate model of the full collimator-detector response. It is shown that the corrective image reconstruction methods provide substantial improvement in ^{111}In PS prostate SPECT image quality.
4. Work has begun to design the evaluation studies using Hotelling and human observers and to generate data for use in these studies.
5. Acquisition of patient data and processing using the corrective image reconstruction methods have begun. Six patient studies have been collected to-date.

REPORTABLE OUTCOMES

Manuscripts

1. Garrity J, Segars WP and Tsui BMW. Development of a Dynamic Model for the Lung Lobes and Airway Tree in the NCAT phantom. IEEE TNS, 50(3): 378-383, 2003.
2. Garrity J, Segars WP and Tsui BMW. Development of a Dynamic Model for the Lung Lobes and Airway Tree in the NCAT phantom. Conference Record of the 2002 IEEE Nuclear Science Symposium and Medical Imaging Conference, Norfolk, VA, November 10-16, 2002.
3. Sayeram S, Tsui BMW, Zhao XD and Frey EC. Performance Evaluation of 3 Different SPECT Systems Used in In-111 ProstaScint SPECT Imaging. Conference Record of the 2003 IEEE Nuclear Science Symposium and Medical Imaging Conference, October 19-25, 2003, Portland, OR.
4. Sayeram S, Tsui BMW, Zhao XD and Frey EC. Performance Evaluation of 3 Different SPECT Systems Used in In-111 ProstaScint SPECT Imaging. Manuscript submitted to IEEE Transactions in Nuclear Science, 2004.

Presentations

1. Sayeram S, Tsui BMW, Zhao XD and Frey EC. Performance Evaluation of three different camera systems Scintillation Crystals used infor 111In-111 Prostascint® SPECT Imaging. Paper presented at the 50th Annual Meeting of the Society of Nuclear Medicine, New Orleans, LA, June 21-25, 2003.
2. Sayeram S, Tsui BMW, Zhao XD and Frey EC. Performance Evaluation of 3 Different SPECT Systems Used in In-111 ProstaScint SPECT Imaging. Paper presented at the 2003 IEEE Nuclear Science Symposium and Medical Imaging Conference, Portland, OR, October 19-25, 2003.
3. Tsui BMW, Zhao X, Frey EC, Shao L, Aarsvold J, Durbin M, Alazraki N and Rollo FD, Evaluation of Quantitative Prostate SPECT/CT using In-111 ProstaScint®. Paper accepted for oral presentation at the 51st Annual Meeting of the Society of Nuclear Medicine, Philadelphia, PA, June 19-23, 2004.

CONCLUSIONS

We have made significance progress in Year 2 of the project. The development of a fast simulation method of realistic ¹¹¹In PS projection data was completed. The method is based on Monte Carlo simulation methods to simulation photon transport inside the phantom and the development of an angular response function (ARF) which accurately models the full imaging characteristics of the collimator-detector response function and is predetermined using Monte Carlo methods. The fast simulation method is 410 times faster than a straight Monte Carlo simulation method and provide the same accuracy and simulated image quality.

We completed the development of corrective image reconstruction methods that incorporate accurate compensation of photon attenuation and scatter in the patient and an accurate model of the full collimator-detector response. It is shown the corrective image reconstruction methods provide substantial improvement in ¹¹¹In PS prostate SPECT image quality.

Work has begun to design the evaluation studies using Hotelling and human observers and to generate data for use in these studies. Acquisition of patient data and processing using the corrective image reconstruction methods have begun. Six patient studies have been collected to-date.

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APPENDICES.